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EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,765	GOZES ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-24 and 26-29* is/are pending in the application.

4a) Of the above claim(s) *2-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 10-24, 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. The Restriction/Election requirement required Applicant to elect one SEQ ID NO to be examined. In the Response, filed 11 April 2006, Applicant elected SEQ ID NO: 2 (NAVSIPQ) and suggested that SEQ ID NO: 2 was readable on claims 1, and 9-28. Upon further consideration, the Examiner will rejoin the species of SEQ ID NOs: 2, 9, 10, 11, and 12, for examination purposes because SEQ ID NOs 9, 10, 11, and 12 are variants of SEQ ID NO: 2 (NAVSIPQ) and they each contain the core sequence of SEQ ID NO: 2.

Formal Matters

2. Applicant's Response and Amendments filed 6 December 2006 are acknowledged. Claims 1-8, 10-24, and 26-29 are pending. Claims 9 and 25 have been cancelled by Applicant. New claim 29 has been added. Claims 2-8 are withdrawn, as being drawn to non-elected inventions. Claims 1, 10-24, and 26-29 are under examination.

Response to Arguments/Amendments

Objections to the Specification - Withdrawn

3. The objection to the disclosure because of the following informalities: the proper phrasing is a claim for benefit, not for priority, is withdrawn in light of Applicant's amendment.

4. The objection to the disclosure because of improper Incorporation by Reference is withdrawn.

Claim Objections/Rejections Withdrawn

5. Claim objections and rejections drawn to claims 9 and 25 are moot in light of Applicant's cancellation of those claims.

6. The objection of claims 1, 14, 17-22 because of the following informalities: the claims contain subject matter directed to non-elected inventions.

Applicant argues that Applicant's are entitled to maintain claims directed to non-elected species and that upon allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species. Applicant's arguments have been fully considered. The objection is withdrawn with the following notation.

Applicant is correct that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a). However, this application contains claims that drawn to an invention non-elected with traverse in Paper No. 15 (filed 11 April 2006). Applicant is advised that a complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. At the present time, no generic claims are allowable.

7. The objection of Claims 15 and 22 because of informalities that the claims contain what appears to be a typographical error due to the phrase "at at," is withdrawn with the following notation. The phrase "at at" in the claim language appears in claims 15 and 22 filed of record on 22 July 2004. The amended claims filed 6 December 2006 have been amended and do not include the full original text of the "at at" claim language that previously appeared in the claim set of 22 July 2004. Applicant is reminded of MPEP 714(c) and 37 CFR 1.121, which states that Amendments to a claim **must be made** by rewriting **the entire claim** with all changes (e.g., additions and deletions) as indicated in this subsection, except when the claim is being canceled [emphasis added].

8. The rejection of claims 1, 10-24, 26-28 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps is withdrawn in light of Applicant's amendments.

9. The rejection of claims 1, 9-11, 14-15, 17, and 20-28 under 35 U.S.C. 102(b) as being clearly anticipated by WO 98/35042 (published 13 August 1998), is withdrawn in light of Applicant's amendments.

10. The rejection of claims 1, 9-11, 14-15, 17, and 20-28 under 35 U.S.C. 102(e) as being clearly anticipated by Gozes et al., US Patent 6,613,740 (2 September 2003, priority to 7 February 1997), is withdrawn in light of Applicant's amendments.

11. The rejection of claims 1, 10-11, 14-17, and 20-24 and 26-28 under 35 U.S.C. 103(a) as being unpatentable over either Gozes et al., US Patent 6,613,740 (2 September 2003, priority to 7 February 1997) or WO 98/35042 (published 13 August 1998), in view of Brenneman et al., (US PreGrant

Publication US 2002/001301 A1, published 15 August 2002), is withdrawn in light of Applicant's amendments.

12. The rejection of claims 15 and 22 rejected as failing to define the invention in the manner required by 35 U.S.C. 112, second paragraph, is withdrawn.

Claim Objections/Rejections Maintained

Claim Rejections - 35 USC § 112, First Paragraph
Scope of Enablement

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. The rejection of claims 1, 10-15, 17-23, 26-28 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating neurologically-related autoimmune diseases by administering to a subject a therapeutically effective amount of the polypeptide consisting of SEQ ID NOs: 2, 9, 10, 11, and 12 (of which SEQ ID NOs: 9, 10, 11, and 12 are variants of the core sequence of SEQ ID NO: 2 (NAVSIPQ)), does not reasonably provide enablement for treating an autoimmune disease by administering the full length ADNF III polypeptide or for preventing an autoimmune disease via administering either the polypeptide of SEQ ID NO:2 or the full length ADNF polypeptide, is maintained for the reasons of record and for the reasons set forth herein.

Applicant argues the Examiner appears to have focused on inoperative embodiments leading to the conclusion that undue experimentation would be required to use the claimed methods. Applicant argues that the specification provides standard assays and working examples for treatment and prevention of multiple sclerosis as well as the minimum core ADNF III sequence required for a beneficial effect. Applicant argues that the recitation of known sequences is not required to meet the enablement standard. Applicant also argues that the specification enables prevention of an autoimmune disease because the specification discloses genetic tests to identify patients that are candidates for multiple sclerosis. Applicant also argues that the specification also discloses tests to determine the efficacy of prevention. Applicant's arguments have been fully considered, but they are not persuasive.

Applicant's claims, as amended, are drawn to a method for administering a pharmaceutical composition comprising a genus of ADNF III polypeptides comprising an active core site comprising the

sequence of SEQ ID NO: 2 (NAPVSIPQ) in a subject to prevent or treat multiple sclerosis. The scope of the claims encompass a method of administering any polypeptide so long as it comprises the core sequence of SEQ ID NO: 2. The instant claims are drawn to a genus of ADNF III polypeptides comprising an active core site comprising SEQ ID NO: 2, which, in preferred embodiments, may encompass up to 44 additional amino acids ("up to about 20 on each of the N-terminus and C-terminus of the core sequence"). This translates into a minimum of 4.4×1.0^{21} possible polypeptides, considering only the standard 20 L-amino acids at each position with an unspecified residue. This number would increase if non-standard amino acids or D-amino acids were added. Applicant has simply not disclosed a sufficient number of representative species of polypeptides comprising SEQ ID NO: 2 such that the person of ordinary skill in the art would know how to make and/or use Applicant's invention. The genus of polypeptides comprising SEQ ID NO: 2 comprises numerous polypeptides of undefined sequence or length. Applicant has not provided sufficient guidance as to how to make or use the genus of ADNF III polypeptides comprising SEQ ID NO: 2 in the instant method. Applicant has also failed to recite the sequence of full-length ADNF III contemplated by the claims. The scope of Applicant's claims, as written, are not commensurate with the scope of what is taught in the specification.

The assertion that the disclosed genus of ADNF III polypeptides with a core active sequence of SEQ ID NO: 2 have biological activities similar to the SEQ ID NO: 2 cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For exemplary purposes only, see Tischer et al. (U.S. Patent 5,194,596), which establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). Additionally, Kopchick et al. (U.S. Patent 5,350,836, cited for exemplary purposes only) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48). Further, Skolnick et al. (2000, Trends in Biotech. 18:34-39) (recited for exemplary purposes only) states that knowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Moreover,

there are inactive ADNF III polypeptides comprising an active core site of SEQ ID NO: 2 that do not maintain the claimed function (see, i.e. SCORE search results 25 April 2006, .rag database, item 41 – WO/200027875, Gozes et al., an 18 amino acid inactive polypeptide comprising SEQ ID NO: 2 at residues 9-18; also recited in the instant specification at paragraph 2). The polypeptide consisting of SEQ ID NOs: 9, 10, 11, and 12 (of which SEQ ID NOs: 9, 10, 11, and 12 are variants of the core sequence of SEQ ID NO: 2 (NAVSIPQ)) appear to have sufficient support in the disclosure because the amino acid residuesof SEQ ID NOs 9, 10, 11, and 12, that differ from the core sequence of SEQ ID NO: 2 are commonly used linker sequences that are old and well known in the art. It is not likely that these linker sequences would impair the biological function of the core sequence because they are known in the art to be closely related to naturally occurring polypeptide linker sequences (see, for exemplary purposes only, Argos. J Mol Biol 1009. 211:943-958.)

Further, it is unclear from the specification that a substitution of an L- for a D-amino acid in the active core site of the ADNF III polypeptide consisting of SEQ ID NO: 2 would retain its functional activity (see claims 12 and 13). Polypeptides have three dimensional structures and altering the chirality of even one amino acid (i.e. from L- to D-) can alter the biological function of polypeptides (see, i.e. Soto et al., J Phys Chem B Condens Matter Mater Surf Interfaces Biophys. 2005 Jan 27;109(3):1281-8, especially abstract). Claim 13, for example, recites that all of the active core site of the ADNF III polypeptide (SEQ ID NO: 2) contains all D-amino acids. There is no teaching in the specification and no guidance provided that would support any biological function for a protein comprising SEQ ID NO: 2 comprising all D-amino acids. It would be undue experimentation to make and test the D-amino acid substitutions for a sufficient number of polypeptides comprising SEQ ID NO: 2, using D-amino acid substitutions. The effects of the D-amino acid substitutions would be unpredictable.

Claims 17-22 are drawn to the method of claim 1 further comprising an ADNF I polypeptide comprising an active core site of SEQ ID NO: 1 (SALLRSIPA). The scope of the claims encompass a method of administering any polypeptide so long as it comprises the core sequence of SEQ ID NO: 1. The instant claims are drawn to a genus of ADNF I polypeptides comprising an active core site comprising SEQ ID NO: 1, which, in claim 22, may encompass up to 44 additional amino acids ("up to about 20 amino acids on each of the N-terminus and C-terminus of the core sequence"). This translates into a minimum of 4.4×1.0^{21} possible polypeptides, considering only the standard 20 L-amino acids at each position with an unspecified residue. The number of possible polypeptides would increase significantly if non-standard amino acids or D-amino acids were added. Applicant has simply not disclosed a sufficient number of representative species of polypeptides comprising SEQ ID NO: 1 such

that the person of ordinary skill in the art would know how to make and/or use Applicant's invention. The genus of polypeptides comprising SEQ ID NO: 1 comprises numerous polypeptides of undefined sequence or length. Applicant has not provided sufficient guidance as to how to make or use the genus of ADNF I polypeptides comprising SEQ ID NO: 1 in the instant method. Applicant has also failed to recite the sequence of full-length ADNF III contemplated by the claims. The scope of Applicant's claims, as written, are not commensurate with the scope of what is taught in the specification.

The assertion that the disclosed genus of ADNF I polypeptides with a core active sequence of SEQ ID NO: 1 have biological activities similar to the SEQ ID NO: 1 cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities (see *supra*). Further, it is unclear from the specification that a substitution of an L- for a D-amino acid in the active core site of the ADNF I polypeptide consisting of SEQ ID NO: 1 would retain its functional activity (see claims 18 and 19). Polypeptides have three dimensional structures and altering the chirality of even one amino acid (i.e. from L- to D-) can alter the biological function of polypeptides (see, i.e. Soto et al., J Phys Chem B Condens Matter Mater Surf Interfaces Biophys. 2005 Jan 27;109(3):1281-8, especially abstract). Claim 19, for example, recites that all of the active core site of the ADNF I polypeptide (SEQ ID NO: 1) contains all D-amino acids. There is no teaching in the specification and no guidance provided that would support any biological function for a protein comprising SEQ ID NO: 1 comprising all D-amino acids. It would be undue experimentation to make and test the D-amino acid substitutions for a sufficient number of polypeptides comprising SEQ ID NO: 1, using D-amino acid substitutions. The effects of the D-amino acid substitutions would be unpredictable.

Regarding Applicant's claims of "prevention," the specification does not reasonably provide any enablement for prevention of multiple sclerosis (MS) in a subject. The skilled artisan cannot envision the prevention of multiple sclerosis. Prevention involves attacking the underlying cause of MS (i.e., disrupting the mechanisms which give rise to MS). In support of Applicant's arguments, Applicant references p. 23, paragraph 79 of the specification, which states that "a majority of MS patients have HLA-type DR2a and DR2b." However, no evidentiary or documentary support is provided (i.e. in the form of a journal reference or experimental data) to substantiate this statement. Although data and references are not required, they are considered helpful in evaluating such statements. More importantly, the statement itself recites that "a majority" of MS patients have this particular MHC class II subtype. There is no evidence in the art or in the specification that shows HLA-DR2a or HLA-DR2b to be the sole factors involved with the onset of multiple sclerosis. In fact, the etiology of MS is still unknown (see, for

exemplary purposes only, Szczucinski et al., Acta Neurol Scand. 2007 Mar;115(3):137-46, Abstract only). The skilled artisan is aware that the causes of multiple sclerosis were unknown at the time of the instant invention. For purposes of enablement, the specification must provide reasonable detail in order for those skilled in the art to carry out the invention. In this case, the specification must disclose a means of preventing multiple sclerosis, regardless of its underlying causes. The teachings of the specification do not enable a person of ordinary skill in the art to make and use the claimed method of prevention.

Due to the large quantity of experimentation necessary to determine whether the genera of polypeptides comprising SEQ ID NO: 2 are effective at treating or preventing MS, a disease for which there is no known etiology, such that it can be determined how to use the claimed methods, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that there are numerous distinct polypeptides comprising SEQ ID NO: 2, and the breadth of the claims which include prevention for a disease with no known etiology, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

15. Claims 1, 10-24, 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are maintained for reasons of record and for the reasons set forth herein.

Applicant argues that the description of the structure of the ADNF III core sequence (i.e. SEQ ID NO:2) and the correlating function (i.e. treatment of multiple sclerosis) are sufficient to adequately describe the claimed genus of ADNF III polypeptides. Applicant also argues that there is no per se requirement regarding the inclusion of sequence information in a patent application to support the written description of a nucleic acid or amino acid sequence. Applicant argues that the genus of ADNF III polypeptides used in the claimed methods is adequately described and that disclosure is not required to demonstrate that the inventor's had possession of the genus at the time of filing. Applicant's arguments have been fully considered, but they are not persuasive.

Contrary to Applicant's arguments, *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim

indicates that these claims are drawn to a genus of ADNF III polypeptides comprising an active core site comprising SEQ ID NO: 2, which, in preferred embodiments, may encompass up to 44 additional amino acids. This translates into a minimum of 4.4×1.0^{21} possible polypeptides, considering only the standard 20 L-amino acids at each position with an unspecified residue. This number would increase if non-standard amino acids or D-amino acids were added, as they are in claims 12 and 13. Claims 17-22 are also drawn to a genus of ADNF I polypeptides comprising an active core site comprising SEQ ID NO: 1, which, in preferred embodiments, may encompass up to 44 additional amino acids. This translates into a minimum of 4.4×1.0^{21} possible polypeptides, considering only the standard 20 L-amino acids at each position with an unspecified residue. This number would increase if non-standard amino acids or D-amino acids were added, as they are in claims 18 and 19. Applicant has also failed to recite the sequence of full-length ADNF III contemplated by the claims. As such, it appears that Applicant was not in possession of the claimed genus at the time the application was filed.

Applicant argues that the core structure of SEQ ID NO:2 and the function of treating MS is sufficient to describe the claimed genus of polypeptides for use in the recited method. This assertion that the disclosed genus of ADNF III polypeptides, with a core active sequence of SEQ ID NO: 2, all have biological activities of treating MS cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. The polypeptide consisting of SEQ ID NOs: 9, 10, 11, and 12 (of which SEQ ID NOs: 9, 10, 11, and 12 are variants of the core sequence of SEQ ID NO: 2 (NAVSIPQ)) are sufficiently disclosed in the specification because their structure is defined and recited and the amino acid residues of SEQ ID NOs 9, 10, 11, and 12, that differ from the core sequence of SEQ ID NO: 2 are commonly used linker sequences that are old and well known in the art.

Moreover, there are known inactive ADNF III polypeptides comprising an active core site of SEQ ID NO: 2 that do not maintain the claimed function (see, i.e. SCORE search results 25 April 2006, .rag database, item 41 – WO/200027875, Gozes et al., an 18 amino acid inactive polypeptide comprising SEQ ID NO: 2 at residues 9-18; also recited in the instant specification at paragraph 2).

The genus of ADNF III polypeptides and the genus of ADNF I polypeptides are highly variable in structure (as shown in the NCBI references recited in the Office Action of 6 July 2006). The structure which is asserted to make up the polypeptide must be clearly and positively specified. The structure must be organized and correlated in such a manner as to present a complete operative embodiment which is adequately described in the specification. The instant disclosure fails to provide an adequate description of a sufficient number of functional ADNF III polypeptides with the requisite core sequence of SEQ ID

NO: 2 and the function of treating MS, as presently claimed. The instant disclosure also fails to provide an adequate description of a sufficient number of functional ADNF I polypeptides with the requisite core sequence of SEQ ID NO: 1 and the function of treating MS, as presently claimed. The general knowledge and level of those of ordinary skill do not supplement the omitted description because specific, not general, descriptions are needed. Thus, one of skill would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

New Claim Rejections – Necessitated by Amendment

Claim Rejections - 35 USC § 112, First Paragraph

Enablement

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 24 is dependent on amended claim 1. Claim 24 recites the method of claim 1 wherein the ADNF polypeptide is administered to prevent multiple sclerosis. Claim 24 is read as the method of claim 1 wherein prevention, but not treatment is contemplated. Claim 24 is entirely unenabled because of the alternative language of claim 1.

The skilled artisan cannot envision the prevention of multiple sclerosis. Prevention involves attacking the underlying cause of MS (i.e., disrupting the mechanisms which give rise to MS). In support of Applicant's arguments, Applicant references p. 23, paragraph 79 of the specification, which states that "a majority of MS patients have HLA-type DR2a and DR2b." However, no evidentiary or documentary support is provided (i.e. in the form of a journal reference or experimental data) to substantiate this

statement. Data and references are not required, but they are considered helpful in evaluating such statements. More importantly, the statement itself recites that "a majority of MS patients" have this particular MHC class II subtype. There is no evidence in the art or in the specification that shows HLA-DR2a or HLA-DR2b to be the sole factors involved with the onset of multiple sclerosis. In fact, the etiology of MS is still unknown (see, for exemplary purposes only, Szczucinski et al., Acta Neurol Scand. 2007 Mar;115(3):137-46, Abstract only). The skilled artisan is aware that the causes of multiple sclerosis were unknown at the time of the instant invention. For purposes of enablement, the specification must provide reasonable detail in order for those skilled in the art to carry out the invention. In this case, the specification must disclose a means of preventing multiple sclerosis, regardless of its underlying causes. The teachings of the specification do not enable a person of ordinary skill in the art to make and use the claimed method of prevention.

18. Claims 1 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 16 is dependent on amended claim 1. Claim 16 is directed to administering the nucleic acid encoding SEQ ID NO: 2 (gene therapy).

The specification does not reasonably provide enablement for gene therapy. Claim 16, as amended, recites the method of claim 1 wherein the ADNF III polypeptide is encoded by a nucleic acid that is administered to the subject. The claim reads on using nucleic acids as gene therapy. Applicant is not enabled for a method of treating or preventing MS by gene therapy. There are many well-documented problems associated with gene therapy, including inefficient gene transfer, host immune response, and the need for tissue-specific targeting (see, for exemplary purposes only, Verma, *et al.*, Nature 18 Sep 1987 389:239-242, especially p. 239, third column, first full paragraph). Verma *et al.*, teach that gene therapy is unpredictable. Therefore, treating or preventing MS by administering nucleic acids as therapeutic antagonists is entirely unpredictable. For these reasons, the Examiner holds that undue experimentation is required to practice the claimed invention. The guidance provided by the specification is not commensurate with the full scope of the claims.

Due to the large quantity of experimentation necessary to determine whether the genera of polypeptides comprising SEQ ID NO: 2 are effective at treating or preventing MS, a disease for which there is no known etiology, such that it can be determined how to use the claimed methods, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that

there are numerous distinct polypeptides comprising SEQ ID NO: 2, and the breadth of the claims which include prevention for a disease with no known etiology, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, First Paragraph
Scope of Enablement

19. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

20. Claims 1 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating multiple sclerosis by administering to a human subject a therapeutically effective amount of a pharmaceutical composition comprising the polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for preventing multiple sclerosis by any means, for treating multiple sclerosis by administering a genus of polypeptides comprising SEQ ID NO: 2, or for inhibiting the proliferation of an immune cell in the subject.

Applicant's claims, as amended, are drawn to a method for administering a pharmaceutical composition comprising a genus of ADNF III polypeptides comprising an active core site comprising the sequence of SEQ ID NO: 2 (NAPVSIPQ) in a subject to prevent or treat multiple sclerosis. The scope of the claims encompass a method of administering any polypeptide so long as it comprises the core sequence of SEQ ID NO: 2. Applicant has simply not disclosed a sufficient number of representative species of polypeptides comprising SEQ ID NO: 2 such that the person of ordinary skill in the art would be able to make and/or use Applicant's invention. The genus of polypeptides comprising SEQ ID NO: 2 comprises 46 distinct polypeptides including a cyclin-dependent kinase modulator-regulated protein, ADNF, human gene KIAA0784, several human ADNF III polymorphic clones, and mouse ADNF III (see, for exemplary purpose only, STN search results). Applicant has not provided any guidance as to how to use non-ADNF III polypeptides comprising SEQ ID NO: 2 in the instant method. The scope of Applicant's claims are not commensurate with the scope of what is taught in the specification.

The specification does not reasonably provide enablement for prevention of multiple sclerosis (MS) in a subject. The skilled artisan cannot envision the prevention of multiple sclerosis. Prevention involves attacking the underlying cause of MS (i.e., disrupting the mechanisms which give rise to MS). In support of Applicant's arguments, Applicant references p. 23, paragraph 79 of the specification, which

states that "a majority of MS patients have HLA-type DR2a and DR2b." However, no evidentiary or documentary support is provided (i.e. in the form of a journal reference or experimental data) to substantiate this statement. Data and references are not required, but they are considered helpful in evaluating such statements. More importantly, the statement itself recites that "a majority of MS patients" have this particular MHC class II subtype. There is no evidence in the art or in the specification that shows HLA-DR2a or HLA-DR2b to be the sole factors involved with the onset of multiple sclerosis. In fact, the etiology of MS is still unknown (see, for exemplary purposes only, Szczucinski et al., Acta Neurol Scand. 2007 Mar;115(3):137-46, Abstract only). The skilled artisan is aware that the causes of multiple sclerosis were unknown at the time of the instant invention. For purposes of enablement, the specification must provide reasonable detail in order for those skilled in the art to carry out the invention. In this case, the specification must disclose a means of preventing multiple sclerosis, regardless of its underlying causes. The teachings of the specification do not enable a person of ordinary skill in the art to make and use the claimed method of prevention.

The specification does not reasonably provide enablement for inhibiting the proliferation of an immune cell in the subject. There is no guidance in the specification to support the breadth of the claimed inhibition of immune cell proliferation. To support the breadth of the claim, the specification would need to show that T-cell, B-cell, NK cell, dendritic cell, eosinophil, basophil, neutrophil, macrophage, mast cell, microglia, and astrocyte proliferation are inhibited by the claimed method. However, the specification fails to provide any guidance regarding the inhibition of proliferation of any immune cell. The only time the phrase "proliferative response" is used in the specification is on p. 31 to refer to splenocytes, which are most likely to be non-typed T- or B-cells, depending on which area of the spleen was examined. As such, it would require undue experimentation to determine which immune cell types are inhibited by the claimed method. Additionally, it would be unpredictable to determine which cell types are inhibited from proliferating, if any, because the Example on pages 30-31 of the specification does not support the conclusion that any specific immune cell type was inhibited from proliferating.

Due to the large quantity of experimentation necessary to determine whether the genera of polypeptides comprising SEQ ID NO: 2 are effective at treating or preventing MS, a disease for which there is no known etiology, such that it can be determined how to use the claimed methods, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that there are numerous distinct polypeptides comprising SEQ ID NO: 2, and the breadth of the claims which

include prevention for a disease with no known etiology, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph
Written Description – New Matter

21. Claims 1 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant's claims, as amended, are drawn to a method for administering a pharmaceutical composition comprising a genus of ADNF III polypeptides comprising an active core site comprising the sequence of SEQ ID NO: 2 (NAPVSIPQ) in a subject to prevent or treat multiple sclerosis and to inhibit the proliferation of an immune cell in the subject.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., genus of ADNF III polypeptides and a genus of immune cells.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the

recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* splenocytes. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described.

The specification does not reasonably provide an adequate description for inhibiting the proliferation of the genus of immune cells in the subject. To support an adequate description for the claim, the specification would need to show that T-cell, B-cell, NK cell, dendritic cell, eosinophil, basophil, neutrophil, macrophage, mast cell, microglia, and astrocyte proliferation are inhibited by the claimed method. The only time the phrase "proliferative response" is used in the specification is on p. 31 to refer to splenocytes, which are most likely to be non-typed T- or B-cells, depending on which area of the spleen was examined. However, there is no description in the specification of what cell type is specifically contemplated by the term "splenocytes." Similarly, there is no description in the specification for inhibiting the proliferation of "an immune cell in a subject." As such, claim 29 contains new matter.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a genus of immune cells. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, Second Paragraph

22. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

23. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites the limitation "[t]he method of claim 9" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 9 has been cancelled by Applicant. In order to expedite prosecution, claim 10 is read as depending from claim 1.

24. Claims 1, 23 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 23 and 24 are dependent on amended claim 1. However, claims 23 and 24 are confusing. Claim 23 recites the method of claim 1 wherein the subject has multiple sclerosis. If an individual already has multiple sclerosis, he or she can not be prevented from having the disease. Because claim 1 is written in the alternative, claim 23 would necessarily limit the population of subjects to those who have already been diagnosed with MS and thus, only the method of treatment would be applicable. However, because of the way claim 1 is written in the alternative, claim 23 is confusing because the independent claim still refers to a method for preventing or treating and thereby treating or preventing multiple sclerosis, in the alternative. Claim 24 recites the method of claim 1 wherein the ADNF polypeptide is administered to prevent multiple sclerosis. Claim 24 is unclear because of the alternative language of claim 1. Claim 24 can be read as the method of claim 1 wherein prevention, but not treatment is contemplated. Claim 24 is also indefinite because it recites "the ADNF polypeptide" when the claim from which it depends (claim 1) refers to a genus of ADNF III polypeptides. It is unclear which one of the genus of ADNF polypeptides is being referred to in claim 24.

Conclusion

NO CLAIM IS ALLOWED.

This action is Non-Final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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